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Cross-Sectional and Longitudinal Association of Non-Exercise Estimated Cardiorespiratory Fitness with Depression and Anxiety in the General Population: the HUNT Study

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ABSTRACT

Background: Cardiorespiratory fitness may help to prevent depression and anxiety. A paucity of literature has considered the relationship between cardiorespiratory fitness (CRF) and the incidence of depression and anxiety. The objective of this study was to investigate cross-sectional and longitudinal associations of estimated cardiorespiratory fitness (CRF) with depression and anxiety.

Methods: This study included middle-aged and older participants from the second (HUNT 2, 1995-1997) and third (HUNT3, 2006-2008) survery of the Nord-Trøndelag Health Study (HUNT). Baseline non-exercise estimated CRF (eCRF) was determined using standardized algorithms. Depression and anxiety were measured using the Hospital Anxiety and Depression Scale. Logistic regression models were used to evaluate the cross-sectional and longitudinal associations between eCRF and depression and anxiety.

Results: In cross-sectional adjusted analysis including those who participated in HUNT2 (n=26,615 mean age 55.7 years), those with medium and high level of eCRF had 21% (OR, 0.79; 95% CI, 0.71-0.89) and 26% (OR, 0.74; 95% CI, 0.66-0.83) lower odds of depression compared to those with low eCRF level, respectively. Longitudinal analysis including those who participated in both HUNT2 and HUNT3 (n=14,020 mean age 52.2 years) found that medium and level of eCRF was associated with 22% (OR, 0.78; 95% CI, 0.64-0.96) and 19% (OR, 0.81; 95% CI, 0.66-0.99) lower odds of depression compared to those with low eCRF level, respectively. CRF was not associated with anxiety, either cross-sectionally or longitudinally.

Conclusion: Our data suggest that a medium and high level of eCRF during late middle age is cross-sectionally and prospectively associated with lower odds of depression. However, our data do not support that eCRF is associated with anxiety. Further studies are warranted to conclude a causal relationship between eCRF and depression.

Keywords: Cardiorespiratory fitness, Depression, Anxiety, Cardiorespiratory fitness, Physical activity, HUNT

1. Introduction

Depression and anxiety are the second and sixth leading cause of disability (Baxter et al., 2014; Sartorius, 2001) in addition to the individual cost, they are also associated with considerable financial burden and healthcare costs (Chisholm et al., 2016). Moreover, anxiety and depression are associated with a higher physical healthcare burden such as cardiovascular disease (CVD) (Correll et al., 2017) and premature mortality (Greden, 2001; Machado et al., 2018; Sartorius, 2001). Clearly, given the substantial individual and societal burden, there is an urgent need to identify risk factor(s) for anxiety and depression (Cuijpers et al., 2012). A recent global meta-analysis of 49 prospective studies demonstrated that higher levels of physical activity (PA) were protective against the emergence of depression (Schuch et al., 2018). A recent cohort study demonstrates that meeting PA guidelines was associated with 44.7% lower odds of a future generalized anxiety disorder (McDowell et al., 2018). A Swedish prospective study involving 25,520 adults shows the dose response-relationship between the duration of PA and lower risk of depression (Hallgren et al., 2019), in addition they report that exceeding the duration of weekly PA recommended for general health (≥300 min per week, or about 40 min per day) was associated with significantly lower risk of depression as compared to those falling below the recommended level (<150 min per week) (Hallgren et al., 2019).

Another key lifestyle risk factor, which has a growing interest, is cardiorespiratory fitness (CRF) which is known to increase with PA (Ross et al., 2016). CRF is a health-related component of physical fitness defined as the ability of the circulatory, respiratory, and muscular systems to supply oxygen during sustained physical activity (Blair et al., 1996). Currently, interest in the relationship between CRF and mental health has emerged. Specifically, epidemiological studies have shown an association between low CRF and symptoms of depression in cross-sectional studies (Suija et al., 2013; Tolmunen et al., 2006) and a small number of prospective studies (Aberg et al., 2012; Dishman et al., 2012; Sui et al., 2009). A recent clinical study showed that the

measured CRF was significantly associated with reduced depression severity in people with depression regardless of exercise intensity and frequency (Rahman et al., 2018). A preliminary meta-analysis of 3 prospective studies demonstrated that people with low CRF and medium CRF have 1.76 and 1.23 higher risk of developing depression (Schuch et al., 2016). However, there are still limited prospective studies addressing the relationship between CRF and depression.

There is a distinct paucity of research considering the association between CRF and anxiety. Only two studies have examined the association of CRF with anxiety (Baumeister et al., 2017; Loprinzi et al., 2017). Whilst some progress has been made, the research to date is limited by small sample sizes and cross-sectional design. Importantly, to the best of our knowledge, no population cohort study has concurrently investigated the cross-sectional and prospective relationship between eCRF and mental health in participants from the same population. Given the aforementioned, the purpose of this study is to examine the relationship between estimated CRF (eCRF) with depression and anxiety cross-sectionally and longitudinally in a representative population of middle-aged and older adults from Norway.

2. Method

2.1. Study cohort

This study uses data from the Norwegian Nord-Trøndelag Health Study (HUNT). The HUNT Study is a large population-based cohort study from the Nord-Trøndelag County. The HUNT Study constitutes a database for medical and health-related research. To date, three health surveys of the general adult population have been undertaken in the Nord-Trøndelag County, Norway HUNT1 in 1984–86, HUNT2 in 1995–97, and HUNT3 in 2006–08.

2.2. Cross-sectional analysis

For the cross-sectional analysis, we included middle-aged and older adult who participated in HUNT2. Among those 42,313 participants (aged 38 and above), we excluded individuals who had missing valid information on Hospital Anxiety and Depression Scale (HADS) scores, on both the anxiety (HADS-A) and depression (HADS-D) subscales or other covariates (n=4113). We further excluded those with missing on the variables included in the algorithm for estimating CRF (n=5670) and those with a history of ischemic heart disease (n=3782) and cancer (n=2133),

because these diseases are suggested to be related to depression or anxiety and/or low CRF. The final cross-sectional analysis included 26,615 individuals (13,708 men and 12,907 women).

2.3. Longitudinal analysis

From the HUNT2 participants included in the cross-sectional analyses, 72% women and 69% men also participated in HUNT3 10-12 years later (n=26,208). In order to examine the longitudinal association of CRF with depression and anxiety, we included only those participants who had valid exposure (eCRF) at baseline (HUNT2) and the outcome of interest (Depression, Anxiety y/n) at follow-up (HUNT3). We excluded those who had HADS-D or HADS-A score ≥ 8 at baseline (HUNT2, n=3346). We further excluded those with a history of ischemic heart disease (n=714), cancer (n=641), and those missing information on exposure, outcome and other covariates (n=7487). The final sample for the longitudinal analysis included 14,020 individuals (7288 men and 6732 women). Flowchart of study participant is presented in Fig 1.

2.4. Estimated cardiorespiratory fitness

The sex-specific algorithms used in our cohort from HUNT2 were developed from data collected in the HUNT Fitness study (2006-2008). This sub-study was designed to obtain normal values from VO_{2peak} in a healthy population through a maximal treadmill test and 4631 participants in the age range 19-90 years participated. The participants also went through clinical examinations and provided self-reported information through several questionnaires as a part of the ordinary HUNT3 study. Because difference questions on physical activity (PA) were used in HUNT1(1984-96) and HUNT2(1995-97), participants in HUNT3 were asked about their PA level by the use of the questions used in the two former HUNT surveys. And for the same reason, it has been developed two different prediction models for non-exercise estimation of CRF from the HUNT population, where one includes the three PA questions on intensity, frequency, and duration used in HUNT1 and HUNT3 (Nes et al., 2011). The other model includes the two PA question from HUNT2 on weekly duration of hard PA (being sweat and breathless) and light PA (not being sweat and breathless) (Nauman et al., 2017). According to the authors (Nauman et al., 2017), the accuracy of the last model is comparable with the first model, and both non-exercise models have been validated against CVD mortality where the results have been published (Nauman et al., 2017; Nes et al., 2014). As the cohort in the current study consists of middle-aged and older people who

participated in HUNT2 we used the sex-specific non-exercise algorithms based on the PA questions from HUNT2. In the current model, PA at 2 levels (where PA=1 if following the current recommendations for PA or 0 if not) meeting or not meeting the weekly current PA recommendations on average over the past year was defined. These PA questions have been validated against directly measured CRF and accelerometer data (Kurtze et al., 2007). The sex-specific model of (eCRF) consists of information about age, waist circumference (WC), PA and resting heart rate (rHR). The following algorithms were used to calculate each individual's eCRF:

Men:
105.91- (0.334*Age) - (0.402*WC) - (0.144*rHR) + (3.102*PA)

Women:
78.00 - (0.297*Age) - (0.270*WC) - (0.110*rHR) + (2.674*PA)

WC circumference was measured to the nearest cm, horizontally at the level of the umbilicus with the participants standing and arms hanging relaxed. The rHR was measured by palpating the radial pulse over a period of 15 seconds with a stop-watch, after at least 4 minutes of seated rest. PA was measured as the weekly average of hours of PA for the last year and was measured through the question "How has your leisure-time physical activity been the last year?" with one answering category for light PA (not being sweat/breathless) and one for moderate/vigorous (being sweat and breathless). The four response options were "none", "less than an hour", "1-2 hours" and "3 hours or more". The participants were classified as physically active if they met the recommended weekly level of 150 minutes of moderate PA, 75 minutes of vigorous PA, or a combination of both. Each participant's eCRF was categorized into age and sex-specific quintiles based on previously published definitions of fitness categories (Blair et al., 1996). Quintile 1 represented low fitness; quintiles 2 and 3, medium fitness; and quintiles 4 and 5, high fitness.

2.5. Assessment of anxiety and depression symptoms

The HUNT surveys included the Norwegian version of the Hospital Anxiety and Depression Scale (HADS) for detecting symptoms of anxiety and depression (Zigmond and Snaith, 1983). The

HADS has been extensively validated in the assessment of symptoms of depression and anxiety severity both in primary health care and in hospital settings (Bjelland et al., 2002; Snaith, 2003). The HADS consists of 7 items that cover anxiety symptoms (HADS-A) and 7 items that cover depressive symptoms (HADS-D). Participants who had responded to less than 5 questions on either the HADS-A or HADS-D scale were excluded from the analyses. From participants who have answered 5 or 6 questions, the total score was extrapolated by multiplying the sum by 7/5 or 7/6, respectively. Scores on the depression and anxiety subscales range from 0 to 21, and increasing score indicates increased symptom load. As recommended in the literature, cut-off for HADS-D and HADS-A score was set at ≥ 8 points (Bjelland et al., 2002). This cut-off is found to give an optimal balance between sensitivity and specificity, at approximately 0.80, both for depression and anxiety according to Diagnostic and Statistical Manual of Mental Disorders (third revised version/fourth version) and International Classification of Diagnoses, 8th/10th edition (ICD-8 and 9) (Mykletun et al., 2007).

2.6. Assessment of covariates

In HUNT2 information was collected using a self-reported questionnaire and clinical measurements, the objective and methods are previously described in detail by Holmen et al (Jostein et al., 2003). Height and weight were measured with the participants wearing light clothes without shoes, height to the nearest 1.0 cm and weight to the nearest 0.5 kg. Resting systolic and diastolic blood pressure was measured by specially trained nurses or technicians using a Dinamap 845XT (Critikon) based on oscillometry. Blood pressure and heart rate were measured automatically three times at one-minute intervals. Blood pressure reported is the mean of the second and third systolic and diastolic blood pressures. Other covariates such as, smoking (current, former, non-smoker), diabetes (yes, no), family history of CVD (no, yes, I don't know), alcohol drinking last 14 days (abstainers, 0 times or not abstainers, 1-4 times, 5 or more times), marital status (unmarried, married, widow, divorced), hypertension (yes, no), limiting long term illness (yes, no). Data on the highest achieved education level was based on the 1995 census and retrieved from the Norwegian Standard Classification of Education by Standard Classification of Education (ISCED-97)(OECD, 2017) to three levels: primary, secondary, and tertiary education level.

2.7. Ethical considerations

Ethical approval for HUNT study was approved from the Data Inspectorate of Norway and recommended by the Regional Committee for Medical Research Ethics. Participants in the HUNT study signed a written consent regarding the use of data for research purpose. The study was conducted in conformity with the Declaration of Helsinki.

2.8. Statistical analysis

Descriptive results regarding the baseline characteristics are reported as mean values (with standard deviations) or percentages across three levels of eCRF. We estimated the cross-sectional and longitudinal association of eCRF with depression and anxiety using binary logistic regression; we calculated odds ratio with 95% confidence intervals for the medium and high category of eCRF, using people with low eCRF as the reference. We also examined eCRF (peak oxygen consumption ml/kg/min) as a continuous and metabolic equivalent (MET) where the odds ratio represents the odds of depression and anxiety associated with a 1-MET (3.5 ml/kg/min) increase in the exposure variable. For these analyses, we used both unadjusted (Model 1) and adjusted models (Model 2-5). In the cross-sectional analysis, four models were tested, and the final model for depression (Table 2, Model 4) was adjusted for sex, marital status, smoking, alcohol intake, education, diabetes, hypertension, limiting long term illness and anxiety score. Similarly, final model for anxiety (Table 2, Model 5) was adjusted for sex, marital status, smoking, alcohol intake, education, diabetes, hypertension, limiting long term illness and depression score. For the longitudinal analysis the final model for depression (Table 5, Model 3) was adjusted for age, sex marital status, smoking, alcohol intake, education, diabetes, hypertension, baseline HADS-D-score and limiting long term illness. Similarly, final model for anxiety (Table 5, model 5) was adjusted for age, sex marital status, smoking, alcohol intake, education, diabetes, hypertension, baseline HADS-A-score and limiting long term illness. Multicollinearity was assessed using variance inflation factor (VIF) and there was no evidence of multicollinearity problem. We tested for multiplicative interactions of eCRF with age and sex; this interaction was not significant in either cross-sectional or longitudinal analyses ($p>0.05$). Statistical significance for all analyses was defined as $P<0.05$. All the statistical analyses were conducted using Stata 10.1 for Windows (Stata Corp, College Station, Texas).

3. Results

Table 1 presents baseline characteristics of study participants stratified by eCRF categories. The mean age (SD) of the participants was 55.7 (SD 11.4) years and 51.5 % were women.

3.1. Cross-sectional association of eCRF with depression

The overall prevalence of depression was 11%. Table 2 presents the cross-sectional association between eCRF and depression and anxiety (separately) using binary logistic regression models. In the fully adjusted model (Model 4), those with medium and high eCRF had 21% (OR; 0.71; 95% CI, 0.71-0.89) and 26% (OR; 0.74; 95% CI, 0.66-0.83) lower odds of depression respectively, compared to those with low eCRF. Test for linear trend suggested a dose-response relationship between level of eCRF and prevalent depression ($p<0.001$).

In the fully adjusted model (Model 4), each 1 MET increase was associated with 11% lower odds of depression (OR; 0.89; 95% CI, 0.86-0.92). Similarly, each 1-unit in peak oxygen consumption increase was associated with 3% lower odds of depression (OR; 0.97; 95% CI, 0.96-0.98).

3.2. Cross-sectional association of eCRF with Anxiety

The overall prevalence of anxiety was 15%. In the multivariable-adjusted model not adjusting for depression, (Table 2, Model 3) those with medium and high eCRF had 10% (OR; 0.90; 95% CI, 0.82-0.99) and 16% (OR; 0.84; 95% CI, 0.76-0.92) lower odds of anxiety respectively, than those who had low eCRF. These inverse associations did not remain statistically significant after further adjustment for limiting long term illness and depression score (Model 5). Test for linear trend did not suggest a dose-response relationship between the level of eCRF and prevalent anxiety ($p=0.125$).

In the multivariable-adjusted model without adjustment for depression score (Table 2, Model 3) each 1 MET increase was associated with 5% lower odds of anxiety (OR; 0.95; 95% CI, 0.92-0.98) and each 1-unit higher in peak oxygen consumption increase was associated with 1% lower odds of anxiety (OR; 0.99; 95% CI, 0.98-0.99). These inverse associations did not remain statistically significant after further adjustment for limiting long term illness and depression score.

3.3. Longitudinal association of eCRF with incident depression

Table 4 presents the characteristics of the mentally healthy study participants stratified by eCRF categories at baseline in HUNT2. The mean age (SD) of participants was 52.2 (9.0) years and 52% were women. During 11 years of follow up 838 incidence cases of depression were identified. The overall cumulative incidence of depression was 59.8 per 1000 person-year.

Table 5 presents the longitudinal association of CRF with incident depression and incident anxiety. There were no sex and age differences in the association between CRF and incident depression and incident anxiety. In the fully adjusted model (Model 3) those with medium and high eCRF had 22% (OR, 0.78; 95% CI, 0.64-0.96) and 19% (OR; 0.81; 95% CI, 0.66-0.99) lower risk of depression than those who had a low eCRF level, respectively. Test for linear trend suggested a dose-response relationship between eCRF and incident depression ($p<0.05$). Each 1-unit higher MET was associated with 8% lower risk of depression (OR; 0.92; 95% CI, 0.86-0.99). Similarly, each 1-unit in peak oxygen consumption increase was associated with 3% lower risk of depression (OR; 0.97; 95% CI, 0.96-0.99).

3.4. Longitudinal association of eCRF with incident anxiety

During 11 years of follow up, there were 1009 incident anxiety events. The overall cumulative incidence of anxiety was 72-per1000 person-year. Table 5 presents the longitudinal association between eCRF and incident anxiety. eCRF, MET and peak oxygen consumption were not significantly associated with incident anxiety in the adjusted analysis.

4. Discussion

In our large cohort study, we observed that medium and high levels of eCRF were associated with a lower risk of depression as compared to those with low eCRF level, even after adjustment for well-known risk factors in both cross-sectional and longitudinal analyses. Specifically, we found 11% and 8% lower risk of depression for each unit increase in MET in cross-sectional and longitudinal data respectively. However, our data do not support a statistically significant association of MET with anxiety neither in cross-sectional analysis nor in longitudinal analysis.

The findings of the present study are in line with previous studies, which demonstrates that higher level of measured CRF is associated with lower odds of depression (Aberg et al., 2012; Schuch et al., 2018; Sui et al., 2007; Willis et al., 2018) even after adjustment of potential confounders such as age, sex, education, alcohol, diabetes, and smoking and limiting long-term illness. Interestingly, in the cross-sectional analyses, eCRF was statistically associated with anxiety until we added depression to the last multivariable model. The latter finding does not correspond to the cross-sectional study of Loprinzi et al. (Loprinzi et al., 2017) who found that those with moderate to high CRF had 46% lower odds of having generalized anxiety, panic, and depressive symptoms compared to those with low CRF. However, as the outcome measure in the study of Loprinzi et al. was made from all of these three mental health disorders the results are not quite comparable, further, the participants in their study were younger (between aged 20 and 39).

In the longitudinal prospective analyses, we found that those with the medium and high level of CRF had a 22% and 19% lower risk of depression as compared to those with a low level of CRF. This finding is consistent with results from the Copper Center Longitudinal Study finding, which reported that high and moderate CRF was associated with a 16% and 8% lower risk of developing depression (Willis et al., 2018). Even the fully adjusted model demonstrated that each unit improvement in peak oxygen consumption was associated with 2-3% lower odds of depression. Given the importance of PA for maintenance of CRF recent longitudinal results from the HUNT study support our findings as they found that 12% of future cases of depression can be prevented by engaging at least 1 hour of PA per week (Harvey et al., 2018). Inconsistent with our finding, Baumeister and colleagues (Baumeister et al., 2017) have reported a 31% lower risk of anxiety disorder per 1-SD increase in peak oxygen uptake in a prospective study with an average 4.5 years of follow-up. This observed difference may be due to the difference in the lengths of follow-up and other methodological differences between the studies. One of the reasons for the lack of statistical significant association of CRF with anxiety in the longitudinal design may be due to the long follow up, as many factors, including variation in physical activity, probably occurred over that period. Moreover, a previous study (Langhammer et al., 2012) shows that the participation in HUNT3 depended on socioeconomic status, chronic diseases (CVD, renal disease, diabetes etc.) and symptoms (chronic musculoskeletal pain, urine incontinence, cough, wheezing etc.) Therefore, those who were older and with comorbidities who also were more likely to have

depression and anxiety were less likely to participate in HUNT3. Furthermore, the association between CRF and mental health is complex, and as previous studies have reported there exist a bidirectional association between PA and mental health (Azevedo Da et al.). In the current study, we found no gender differences regarding the relationship between CRF with depression and anxiety.

Physiological mechanisms associating CRF with depression are not fully understood. However, some possible explanation can be due to PA associated with functional connectivity of brain regions (Ferris et al., 2007; Russo-Neustadt et al., 2000; Thoren et al., 1990). Specifically, aerobic exercise interventions that stimulate CRF have been found to be associated with greater hippocampal volume (Firth et al., 2018), an area which is typically decreased in those with depression. (Campbell and MacQueen, 2004). Exercise can increase the release of brain neurotransmitters such as monoamine and endorphins or neurotrophic factors (Russo-Neustadt et al., 2000; Thoren et al., 1990), which are the important factor that provides antidepressant effects by enhancing endothelial function, inhibiting cell death, neurogenesis and by cell proliferation (Firth et al., 2018).

In this study, both cross-sectional and longitudinal analyses showed that individuals with medium and high level of CRF estimated by using easily available health indicator variables had lower odds of depression compared to those with low CRF. However, in contrast to other published results, our findings do not support an association between CRF and anxiety. This needs further investigation. Still, findings from our study and others (Schuch et al., 2016; Sui et al., 2007) support the notion that CRF can be a potential target for preventing depression. Exercise should be promoted to maintain high CRF as there is evidence from the meta-analysis that exercise intervention can improve CRF among people experiencing depression (Stubbs et al., 2016). Taken together, the finding of our study suggest that maintaining medium and high levels of CRF can protect the future risk of depression in the general population.

4.1. Strength and Limitations

The main strength of the present study is its cross-sectional and longitudinal design to study the association of CRF with both depression and anxiety in a representative sample from the same

population-based cohort. Our study has a relatively long follow-up and we take into account a wide range of potential confounders. Additionally, the HUNT cohort is recognised for having valid data and a very high participation rate (Krokstad et al., 2013). Furthermore, eCRF was calculated using non-exercise algorithms developed from the same cohort, which can provide valid estimates of CRF. However, our study has several limitations. Most of the covariates were self-reported leaving open for the possibility of residual confounding. The HADS score is designed to assess symptoms, not a gold standard clinical diagnosis of depression and anxiety, further the predicted CRF score is based on self-reported PA data. In addition, we cannot separate the beneficial effect of fitness from different level of PA because we can't adjust the PA variable in the model due to its function in the calculation of eCRF. Further studies measuring objectively PA and CRF are needed to explore this association. As the population of HUNT study is quite homogeneous with respect to ethnicity and genetics, the findings of this study have high internal validity, but this may limit generalization to other populations.

5. Conclusions

Estimated CRF was cross-sectionally and prospectively associated with lower risk of depression but not with anxiety. Population-based interventions designed to reduce depression risk should promote PA to increase or maintain CRF levels. More research on the association between non-exercise estimated fitness and anxiety is needed.

Author Contributions: Shigdel and Ernstsen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Shigdel and Ernstsen
Acquisition, analysis, or interpretation of data: Shigdel, Ernstsen, Stubbs, Xumei Sui
Drafting of the manuscript: Shigdel
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: Shigdel
Obtained funding: Ernstsen

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Table 1 Baseline characteristic of study participants stratified by eCRF categories in the HUNT2 study (1995-1997) included in the cross-sectional study (n =26,615)

Baseline characteristics	Total	Low eCRF Level	Medium eCRF Level	High eCRF Level
	n(%) or mean ±SD	n(%) or mean ±SD	n(%) or mean ±SD	n(%) or mean ±SD
Sex				
Women	13,708 (51.5)	2,699 (51.4)	5,447 (52.4)	5,562 (51.4)
Men	12,907 (48.5)	2,549 (48.57)	5,156 (48.6)	5,202 (48.6)
Age in years	55.7 (11.4)	56.79 (11.3)	56.0 (11.3)	55.0 (11.4)
Height (CM)	170.0 (9.1)	170.5 (9.5)	170.3 (9.1)	169.5 (8.9)
Weight (Kg)	77.2 (13.6)	89.7 (13.9)	78.01 (11.3)	70.1 (10.5)
BMI (Kg/m^2)	26.6 (3.9)	30.9 (4.2)	26.8 (2.9)	24.3 (2.6)
WC (CM)	87.5 (11.3)	100.1 (9.7)	88.6 (8.4)	80.2 (8.4)
eCRF (peak oxygen consumption mL/kg/min)	37.0 (7.7)	30.6 (6.6)	36.1 (6.4)	41.0 (6.9)
HADS-Depression score	3.7 (3.1)	4.1 (3.3)	3.7(3.0)	4.1(3.2)
HADS-D ≥ 8				
No	23,437 (88.1)	4,429 (84.4)	9,358 (88.3)	9,650 (89.65)
Yes	3,178 (11.9)	819 (15.6)	1,245 (11.7)	1,114 (10.3)
HADS-Anxiety score	4.1(3.3)	4.2 (3.5)	4.1 (3.3)	4.1 (3.2)
HADS-A ≥ 8				
No	22,652 (85.1)	4,383 (83.5)	9,014 (85)	9,255 (86)
Yes	3,963 (14.9)	865 (16.5)	1,589 (15)	1,509 (14)
eCRF (MET)	10.6 (2.2)	8.7 (1.9)	10.3 (1.8)	11.7 (1.9)
Smoker n (%)				
Current	7,752 (29.1)	1,523 (29.0)	3,129 (29.5)	3,100 (28.8)
Former	8,266 (31.0)	1,809 (34.5)	3,413 (32.2)	3,044 (28.3)
Non smoker	1,0597 (39.8)	1,916 (36.5)	4,061 (38.3)	4,620 (42.9)
Alcohol consumption, n (%)				
Abstainers	3,327 (12.5)	802 (15.3)	1,345 (12.7)	1,180 (10.9)
0 times, not abstainers	7,638 (28.7)	1,701 (32.4)	3,065 (28.9)	2,872 (26.7)
1-4 times	12,807 (48.1)	2,318 (44.1)	5,130 (48.4)	5,359 (49.8)
5 or more times	2,843 (10.7)	427 (8.1)	1,063 (10.0)	1,353 (12.6)
Diabetes mellitus, n (%)				
No	25,884 (97.2)	4,968 (94.7)	10,320 (97.3)	10,596 (98.4)
Yes	731 (2.7)	280 (5.3)	283 (2.7)	168 (1.6)
Hypertension, n (%)				

No	12,966 (48.7)	1,676 (31.9)	4,854 (45.8)	6,436 (59.7)
Yes	13,649 (51.3)	3,572 (68.1)	5,749 (54.2)	4,328 (40.2)
Education, n (%)				
Primary	8,156 (30.6)	1,962 (37.4)	3,369 (31.8)	2,825 (26.2)
Secondary	13,849 (52.0)	2,710 (51.6)	5,588 (52.7)	5,551 (51.6)
Tertiary	4,610 (17.3)	576 (10.9)	1,646 (15.5)	2,388 (22.2)
Marital status, n (%)				
Un married	2,002 (7.5)	519 (9.9)	695 (6.5)	788 (7.3)
Married	20,111 (75.6)	3,784 (72.1)	8,121 (76.6)	8,206 (76.2)
Widow	2,269 (8.5)	507 (9.7)	917 (8.6)	845 (7.8)
Divorced	2,233 (8.4)	438 (8.3)	870 (8.2)	925 (8.6)
Limiting long term illness (n=25,154)				
No	18,372 (73)	3,192 (65.3)	7,243 (72,3)	7,937 (77.4)
Yes	6,782 (27)	1,695 (34.7)	2,769 (27,7)	2,318 (22.6)

eCRF=estimated cardiorespiratory fitness; BMI =body mass index; WC=waist circumference; MET = metabolic equivalent; HADS–D=Hospital Anxiety and Depression Scale, depression items; HADS–A=Hospital Anxiety and Depression Scale, anxiety items

Values are presented as mean, standard deviation (SD), Number (n), Percentage (%) of participants

Table 2. Cross-sectional association between eCRF and depression, and anxiety for those participated in HUNT2 (1995-1997) (n=26,615).

		HADS-D ≥8 (n = 3,178)			
		Odds ratio (95% CI)			
eCRF	*Events*	*Model 1*	*Model 2*	*Model 3*	*Model 4*
Low (n = 5,248)	819	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Medium (n = 10,603)	1,245	0.73 (0.66-0.79)	0.75 (0.69-0.83)	0.74 (0.67-0.81)	0.79 (0.71-0.89)
High (n = 10,764)	1,114	0.62 (0.56-0.69)	0.69 (0.63-0.76)	0.66 (0.60-0.73)	0.74 (0.66-0.83)
P linear trend		P < 0.001	P < 0.001	P < 0.001	P < 0.001
Per 1 MET		0.90 (0.88-0.91)	0.88 (0.86-0.91)	0.87 (0.84-0.86)	0.89 (0.86-0.92)
eCRF (peak oxygen consumption mL/kg/min)		0.97 (0.96-0.97)	0.96 (0.96-0.97)	0.96 (0.95-0.97)	0.97 (0.96-0.98)
		HADS-A ≥8 (n =3,963)			
eCRF	*Events*	*Model 1*	*Model 2*	*Model 3*	*Model 5*
Low (n = 5,248)	865	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Medium (n = 10,603)	1,589	0.89 (0.82-0.98)	0.91 (0.83-0.99)	0.90 (0.82-0.99)	0.96 (0.87-1.16)
High (n = 10,764)	1,509	0.83 (0.75-0.90)	0.86 (0.78-0.94)	0.84 (0.76-0.92)	0.92 (0.83-1.02)
P linear trend		P < 0.001	P < 0.001	P < 0.05	P =0.125
Per 1 MET		0.94 (0.93-0.96)	0.96 (0.93-0.99)	0.95 (0.92-0.98)	0.98 (0.95-1.01)
eCRF (peak oxygen consumption mL/kg/min)		0.98 (0.98-0.99)	0.99 (0.98-0.99)	0.99 (0.98-0.99)	0.99 (0.99-1.00)

eCRF=estimated cardiorespiratory fitness; MET=metabolic equivalent; CI=confidence interval; HADS–D=Hospital Anxiety and Depression Scale, depression items; HADS–A= Hospital Anxiety and Depression Scale, anxiety items

Model 1: Unadjusted

Model 2: Adjusted for age, sex, marital status, smoking, alcohol intake, education

Model 3: Model 2 + diabetes, hypertension,

Model 4: Model 3 + anxiety, limiting long term illness

Model 5: Model 3 + depression, limiting long term illness

Table 4. Characteristic of the study participants free from depression and anxiety (score ≤ 8) at baseline in HUNT2 (1995-1997) stratified by eCRF categories for the longitudinal analysis (n =14,020)

Baseline characteristics	Total	Low eCRF Level	Medium eCRF Level	High eCRF Level
	n(%) or mean ±SD	n(%) or mean ±SD	n(%) or mean ±SD	n(%) or mean ±SD
Sex				
Women	7,288 (52.0)	1,340 (51.4)	2,870 (51.8)	3,078 (52.4)
Men	6,732 (48.0)	1,266 (48.6)	2,666 (48.2)	2,800 (47.6)
Age	52.2 (9.0)	53.1 (8.9)	52.6 (9.1)	51.5 (8.9)
Height (CM)	170.8 (8.9)	171.5 (9.2)	171.1 (8.9)	170.3 (8.8)
Weight (Kg)	77.3 (13.2)	89.6(13.5)	78.4 (11.2)	70.8 (10.3)
BMI (Kg/m^2)	26.4 (3.7)	30.4 (4.1)	26.7 (2.8)	24.3 (2.4)
WC (CM)	86.4 (10.9)	98.6 (9.3)	87.7 (8.3)	79.7 (8.3)
eCRF (peak oxygen consumption mL/kg/min)	38.7 (7.0)	32.5 (5.8)	37.7 (5.8	42.4 (6.3)
eCRF (MET)	11.1 (2.0)	9.3 (1.7)	10.8 (1.6)	12.1 (1.8)
Smoker n (%)				
HADS-Depression score	2.7 (2.0)	2.8 (1.9)	2.7 (2.0)	2.6 (2.0)
HADS-Anxiety score	3.1 (2.1)	2.9 (2.1)	3.1 (2.1)	3.1 (2.1)
Current	3,675 (26.2)	715 (2749)	1,495 (27.0)	1,465 (24.9)
Former	4,345 (31.0)	910 (34.9)	1,788 (32.3)	1,647 (28.0)
Non smoker	6,000 (42.8)	981 (37.6)	2,253 (40.7)	2,766 (47.1)
Alcohol consumption, n (%)				
Abstainers	1,288 (9.2)	284 (10.9)	519 (9.3)	485 (8.3)
0 times, not abstainers	3,616 (25.8)	806 (30.9)	1,487 (26.9)	1323 (22.5)
1-4 times	7,475 (53.3)	1,288 (49.4)	2,931 (52.9)	3,256 (54.4)
5 or more times	1,641 (11.7)	228(8.7)	599 (10.9)	814 (13.8)
Diabetes mellitus, n (%)				
No	13,796 (98.4)	2,520 (96.7)	5,454 (98.5)	5,822 (99)
Yes	258 (1.6)	86 (3.3)	82 (1.5)	56 (1.0)
Hypertension, n (%)				
No	7,805 (55.7)	969 (37.2)	2,911 (52.6)	3,925 (66.8)
Yes	6,215 (44.3)	1,637 (62.8)	2,625 (47.4)	1,953 (33.2)
Education, n (%)				
Primary	3,210 (22.9)	727 (27.9)	1,345 (24.3)	1,345 (24.3)
Secondary	7,868 (56.1)	1,518 (58.2)	3,174 (57.3)	3,174 (57.3)
Tertiary	2,942 (21.0)	361 (13.8)	1,017 (18.4)	1,017 (18.4)

Marital status, n (%)				
Un married	953 (6.8)	220 (8.4)	344 (6.2)	389 (6.6)
Married	11,339 (80.9)	2,037 (78.2)	4,515 (81.6)	4,787 (81.4)
Widow	635 (4.5)	138 (5.3)	259 (4.7)	237 (4.0)
Divorced	1,094 (7.8)	211 (8.1)	418 (7.6)	465 (7.9)
Limiting long term illness (n=13,502)				
No	10,848 (80.2)	1,832 (73.9)	4,211 (78.8)	4,805 (84.3)
Yes	2,672 (19.8)	645 (25.1)	1,131 (212)	896 (15.7)

eCRF=estimated cardiorespiratory fitness; BMI =body mass index; WC=waist circumference; MET=metabolic equivalent; HADS–D=Hospital Anxiety and Depression Scale, depression items; HADS–A=Hospital Anxiety and Depression Scale, anxiety items.
Values are presented as mean, standard deviation (SD), Number (n), Percentage (%) of participants

Table 5. Associations between baseline eCRF in HUNT2 (1995-1997) with depression and anxiety identified in HUNT3 (2006-2008) (n=14,020).

N=14020		**HADS-D ≥8 (n=838)**		
		Odds Ratio (95% CI)		
eCRF	Events	Model 1	Model 2	Model 3
Low (n = 2,606)	195	1 (Ref)	1 (Ref)	1 (Ref)
Medium (n = 5,536)	331	0.79 (0.65-0.94)	0.82 (0.68-0.99)	0.78(0.64-0.96)
High (n =5,878)	312	0.69 (0.57-0.83)	0.79 (0.65-0.97)	0.81(0.66-0.99)
P linear trend		P < 0.001	P < 0.001	P < 0.05
Per 1 MET		0.94 (0.91-0.98)	0.92 (0.86-0.98)	0.92 (0.86-0.99
eCRF (peak oxygen consumption mL/kg/min)		0.98 (0.97-0.99)	0.97 (0.96-0.99)	0.97 (0.96-0.99)
		HADS-A ≥8 (n =1009)		
		Odds Ratio (95% CI)		
eCRF	Events	Model 1	Model 4	Model 5
Low (n = 2,606)	186	1 (Ref)	1 (Ref)	1 (Ref)
Medium (n = 5,536)	393	0.99 (0.83-1.19)	0.96 (0.79-1.15)	0.94 (0.77-1.14)
High (n = 5,878)	430	1.03 (0.86-1.23)	0.99 (0.82-1.21)	0.99(0.86-1.21)
P linear trend		P =0.708	P =0.881	P=0.855
Per 1 MET		0.93 (0.90-0.96)	1.00 (0.94-1.07)	1.00 (0.94-1.07)
eCRF (peak oxygen consumption mL/kg/min)		0.98 (0.97-0.99)	1.00 (0.98-1.01)	1.00 (0.98-1.01)

eCRF=estimated cardiorespiratory fitness; MET=metabolic equivalent; CI=confidence interval; HADS–D=Hospital Anxiety and Depression Scale, depression items, HADS–A=Hospital Anxiety and Depression Scale, anxiety items

Model 1: Unadjusted

Model 2: Adjusted for age, sex, marital status, smoking, alcohol intake, education, diabetes, hypertension HADS-D at baseline

Model 3: Adjusted for Model 2 + limiting long term illness

Model 4: Adjusted for age, sex, marital status, smoking, alcohol intake, education, diabetes, hypertension HADS-A at baseline

Model 5: Adjusted for Model 4 + limiting long term illness

Figure 1. Participant flow chart for longitudinal study